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The Unmet Residual Factor For Coronary Artery Disease (CAD):Lipoprotein(a)

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains a formidable global health challenge, constituting a leading cause of mortality and morbidity. Atherogenic dyslipidemia, a modifiable risk factor for ASCVD, can be effectively managed with safe and efficient measures, improving patient outcomes. However, a considerable portion of the ASCVD risk remains elusive, and one contributor to this enigma is the perplexing entity known as lipoprotein little ”a” or Lp(a).

Extensive research, drawing from genetic, observational, and pathophysiologic studies, has linked Lp(a) to both the residual ASCVD risk and the occurrence of premature ASCVD. This lipoprotein, which garners limited attention in clinical practice, plays a significant role in the development of ASCVD, specifically in cases of premature ASCVD, calcific aortic valve stenosis (CAVS), and strokes.

Notably, Lp(a) might serve as the missing piece of the puzzle when it comes to explaining the high prevalence of premature and severe forms of ASCVD in the Indian population.

HISTORY

It was first discovered by Norwegian physician Kare Berg in 1963 during his exploration of lipoproteins. His revelation of a new antigen associated with low-density lipoproteins (LDLs) led to the birth of Lp(a).[1] It has high inheritance accounting for a significant portion of cholesterol content in the bloodstream which is particularly relevant today when extremely low LDL-cholesterol (LDL-C) levels are targeted.

STRUCTURE, FUNCTION AND PATHOPHYSIOLOGY

It has a complex structure and functions. Composed of an LDL particle with apoB-100 and a glycoprotein, apo(a). Apo(a) consists of unique loop-like structures known as kringles, which structurally resemble plasminogen. This glycoprotein is produced in the liver and is linked to apoB-100 through a disulfide bond.

Lp(a) has remarkable ethnic variability in serum levels across individuals. For example, Africans generally exhibit 2- to 3-fold higher Lp(a) levels compared to Europeans and many Asian populations.

Lp(a) is a versatile molecule with three primary functions: it promotes atherogenesis, induces inflammation, and triggers blood clot formation. Additionally, Lp(a) has been associated with wound healing and tissue repair.Recent studies also suggest that Lp(a) carries oxidized phospholipids (OxPLs), which are pro-inflammatory and contribute to atherosclerosis.[2] It may have favorable biological effects, such as aiding cell regeneration and organism recovery after injury. Some studies even suggest that low Lp(a) levels could improve survival by reducing cancer mortality.

CLINICAL STUDIES

Elevated Lp(a) levels are typically defined as >30-50 mg/dL or >75-125 nmol/L and affect roughly 20-30% of the global population. In patients with established ASCVD and those at high risk, the prevalence of elevated Lp(a) is even higher.[3]

Several clinical studies have provided robust evidence linking elevated Lp(a) to an increased risk of ASCVD. Importantly, this risk seems to persist even when other risk factors are well managed and when LDL-cholesterol (LDL-C) levels are within target ranges. This raises the question of whether Lp(a) should be considered an ”independent” risk factor.

There is a direct causal relationship between Lp(a) and coronary artery disease (CAD) based on Mendelian randomization studies. Further studies have shown that elevated Lp(a) poses a higher risk for acute myocardial infarction (heart attacks), particularly among younger individuals. Elevated Lp(a) is also associated with an increased risk of heart failure and cerebrovascular diseases, particularly strokes both ischemic and hemorrhagic, with the risk being especially prominent in younger individuals, highlighting the role of Lp(a) in premature strokes.

LABORATORY ESTIMATION OF LP(a)

Measuring Lp(a) demands fresh plasma due to the sensitivity of lipoprotein particles to oxidation. Additionally, the "isoform-insensitive enzyme-linked immunosorbent assay (ELISA)," a more standardized method for Lp(a) measurement, is recommended, as it delivers more consistent results.

One of the challenges in Lp(a) assessment is the variability in particle size, which can influence its functional properties. Smaller isoforms of Lp(a) are associated with a higher risk of ASCVD and they deteriorated significantly than larger isoforms in specimens stored over a while. So Lp(a) assessment should be done in fresh plasma.

LP(a) LOWERING VERSUS LDL-C LOWERING

While both LDL-C and Lp(a) are involved in ASCVD, they have different impacts on risk reduction. Mendelian randomization studies based on a UK database have quantified the risk reductions associated with lowering LDL-C and Lp(a). [4]A 10 mg/dL reduction in LDL-C is estimated to decrease the risk of ASCVD by approximately 14.5%. In contrast, a similar reduction in Lp(a) leads to a smaller reduction in risk, around 5.8%. This underscores the need for therapies specifically targeting Lp(a) to complement existing strategies focused on lowering LDL-C.

THERAPEUTICS

Niacin reduces Lp(a). Two major studies, Aim High and HPS-Thrive showed no significant benefit with Niacin. [5, 6] Recent interest in Lp(a) has been rekindled by the PCSK9 inhibitors reducing Lp(a) by about 25%(evolocumab and Alirocumab). However, when baseline Lp(a) was >50 mg%, the association between Lp(a) reduction and MACE remained significant.

CETP inhibitor Anacetrapib reduced Lp(a) by nearly 35%. [7] A phase-II trial assessed the effect of IONIS-APO(a) Rx, an oligonucleotide targeting apolipoprotein(a) in participants with elevated Lp(a) levels. It reduced Lp(a) by 66-92%, with no serious side effects. The study also showed a significant reduction in LDL-C, apolipoprotein B (apoB), and OxPLs associated with apoB and apo(a). [8]

PLASMA LP(a) APHERESIS

Lipoprotein apheresis is an extracorporeal method that decreases LDL-C and Lp(a), the apoB100-containing particles. There are several methods available and all of them reduce LDL-C and Lp(a) by about 60-70%. Since both Lp(a) and LDL-C increase again quickly, lipoprotein apheresis has to be repeated usually weekly. Apheresis has beneficial effects on endothelial function and myocardial perfusion in a high Lp(a) group of patients.

Lipoprotein apheresis is generally well tolerated and safe, though the process is time-consuming, expensive and there are only a few specialized centers.

WHAT DO GUIDELINES/STATEMENTS SAY?

Recommendations by the Lipid Association of India (LAI) suggests that: Estimation of Lp(a) levels is strongly recommended for ASCVD risk stratification in Indian subjects, particularly in those who have a family history or premature CAD, a level >20 mg/dL indicates increased ASCVD risk. [9] In Indians, it is recommended to use an assay that is unaffected by the isoform size, lipoprotein(a) $\geq$50 mg/dL is a high risk feature, lipoprotein(a) 20-49 mg/dL is a moderate risk non conventional risk factor.

THERAPIES TO LOWER LP(a)

Currently, there are no approved pharmaceutical therapies designed exclusively to target Lp(a). But in clinical practice, patients with elevated Lp(a) levels are managed through a combination of strategies: Therapeutic lifestyle changes, management of other ASCVD risk factors to counter the multiplicative risk effect of elevated Lp(a), achieve recommended LDL-C goals with statins and if required ezetimibe and PCSK9 inhibitors, Lp(a) apheresis to be instituted wherever feasible.

CONCLUSION

The genetic revelations and the mounting evidence of its direct causative role in ASCVD have marked two golden eras. Presently, we stand on the verge of a third golden era, where we anticipate the development of safe and effective therapies aimed at lowering Lp(a) levels. This holds the potential to significantly reduce the residual risk of ASCVD, especially in cases of premature ASCVD and severe cardiovascular conditions.

REFERENCES

1. Berg K. A new serum type system in man-the Lp system. Acta Pathol Microbiol Scand. 1963;59(3):369–82.
2. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol. 2017;69(6):692–711.
3. Nordestgaard BG, Chapman MJ, Ray K. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844–53.

4. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein (a)-lowering therapies: a Mendelian randomization analysis. JAMA cardiology. 2018;3(7):619–627.

5. Landray MJ, Haynes R, Hopewell JC. Effects of extended-release niacin with laropiprant in high risk patients. N Engl J Med. 2014;317(3):203–215.

6. Boden WE, Probstfield JL, Anderson T. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–67.

7. Cannon CP, Shah S, Dansky HM. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl Med. 2010;363:2406–2421.

8. Viney NJ, Capelleveen JCV, Geary RS. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016;388:2239–53.

9. Iyengar SS, Puri R, Narasingan SN. Lipid association of India expert consensus statement on management of dyslipidemia in Indians 2016: Part 1-executive summary. Journal of Clinical and Preventive Cardiology. 2016;5(2):51–61.

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